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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte GARY E. BORODIC

Appeal 2008-2452[1]
Application 09/382,837
Technology Center 1600

Decided: September 15, 2008

Before DONALD E. ADAMS, LORA M. GREEN, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims 1, 5-8, 10-12, 24, 25, and 42-57, the only claims pending in this application (App. Br. 2). We have jurisdiction under 35 U.S.C. § 6(b).

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[1] Heard August 13, 2008.

INTRODUCTION

The claims are directed to a method of reducing inflammation (claims 1, 5-8, 50, 54, and 55); a method for treating allergic blepharoconjunctivitis (claims 10-12, 42-45, 52, and 53); and a method for treating inflammation (claims 24, 25, 46-49, 51, 56, and 57). Claims 1, 10 and 12 are illustrative:

1. A method of reducing inflammation, comprising the step of administering a therapeutically effective dose of a botulinum toxin to an affected area of a subject suffering from inflammation, wherein the botulinum toxin reduces at least one symptom of inflammation, and wherein said therapeutically effective dose is sufficient to reduce said at least one symptom of inflammation but less than a dose necessary to produce substantial muscle weakness within the affected area.

10. A method for treating allergic blepharoconjunctivitis comprising the step of administering a therapeutically effective dose of a botulinum toxin in a periocular area of a subject suffering from blepharoconjunctivitis, thereby reducing inflammation.

12. A method [for treating classic type 1 hypersensitivity comprising the step of administrating a botulinum toxin to an affected area of a subject suffering from classic type 1 hypersensitivity, thereby reducing inflammation], wherein the hypersensitivity is hay fever, rhinitis, allergic rhinitis, allergic forms of eczema, urticaria, rheumatoid arthritis, inflammatory bowel disease, or asthma.

The Examiner relies on the following prior art references to show unpatentability:

First	US 6,063,768	May 16, 2000

The MERCK MANUAL of DIAGNOSIS AND THERAPY (MERCK) pp. 318-320, 1308-1311, and 2368 (sixteenth ed., Robert Berkow et al., eds, MERCK Research Laboratories, Rahway, N.J. 1992).

The rejections as presented by the Examiner are as follows:

1. Claims 1, 5-8, 24, 25, 42, 43, and 46-57 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

2. Claims 1, 5-8, 10-12, 24, 25, and 42-57 stand rejected under the written description provision of 35 U.S.C. § 112, first paragraph.

3. Claims 10-12 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of First and MERCK.

We reverse the rejections under the enablement and written description provisions of 35 U.S.C. § 112, first paragraph.

We affirm the rejection of claims 10-12 under 35 U.S.C. § 103(a) as unpatentable over the combination of First and MERCK. However, because our rationale differs from that of the Examiner we affirm the rejection as a new ground of rejection. 37 C.F.R. § 41.50(b).

FINDINGS OF FACT (FF)

1. Appellant discloses "that the use of botulinum toxin in doses from 1/3rd to several orders of magnitude less than those associated with treatment of regional movement diseases has been effective to reduce inflammation and adverse sensory experiences associated with the inflammatory response" (Spec. 4-5).
2. Appellant discloses that "botulinum toxin in low dosages [in the range from 0.5-5 units] are effective anti-inflammatory agents. Typical minimum effective doses range from 0.5-5 units as opposed to 20-600 units used for treatment of movement disorders" (Spec. 5). Appellant discloses that a dosage range of 0.6 - 15 units is "lower than that required to produce regional [muscle] weakness" (Spec. 20).

3. First teaches a method wherein "at least one serotype or a combination of serotypes of Botulinum neurotoxin either alone or in combination with other peptides or fusion proteins" are "administered in a safe and effective amount, [to] antagonize and therefore decrease or block inflammation induced by the neurogenic mechanisms underlying or associated with inflammatory disorders" (First, Abstract).
4. First teaches that "[a] neurogenic disorder involves the release of neuropeptides, neuromodulators and other mediators of the neurogenic response including mediators from the immune nervous and endocrine systems" (First, col. 2, ll. 56-59).
5. First teaches that "[t]he present invention provides a method of treating or inhibiting diseases or syndromes with an underlying or associated neurogenic component (neurogenic disorder) by way of antagonizing the actions of neurogenic mediators involved in the disorder" by administering botulinum toxin in "a safe and effective amount . . . at or near the site of inflammation" (First, col. 5, ll. 15-19; col. 7, ll. 32-35).
6. First teaches that the method antagonizes "the release or enzymati [sic], cleave neuropeptides, neurotransmitters and other mediators from, in particular, sensory afferent or efferent neurons, autonomic efferent nerves or secretory cells" (First, col. 1, ll. 19-22).
7. First teaches that "[t]he responses mediated by the peptides and transmitters released from sensory nerves include vasodilatation (via cGRP release), and increased vascular permeability (via SP [(Substance P)[2]] release)" (First, col. 2, ll. 33-36).

[2] *See* First, col. 3, l. 3.

8. First teaches that "the activation of the immune system initiates the attraction of white cells, activation of phagocytic function of neutrophils and macrophages, stimulation of the increased production and release of inflammatory mediators from these cells and the degranulation of mast cells and local release of histamine" (First, col. 2, ll. 39-44).

9. First teaches that

> Substance P has been shown to stimulate the release of prostaglandin E2 and collagenase from cells in joints of patients with rheumatoid arthritis . . ., and further, induce the release of immune-active agents such as interleukin 1, tumor necrosis factor and interleukin 6. . . . The result of this neuroendocrine cascade of events has been termed, neurogenic inflammation . . . and works as a central network modulating the events between the immune, nervous and endocrine systems. A neurogenic disorder involves the release of neuropeptides, neuromodulators and other mediators of the neurogenic response including mediators from the immune nervous and endocrine systems.

(First, col. 2, ll. 47-59.)

10. First teaches that "SP and cGRP are both released from afferent sensory neurons that carry sensory information back to the central nervous system" (First, col. 3, ll. 64-66).

11. First hypothesizes that botulinum neurotoxin "acts enzymatically to cleave either proteins such as SNAP-25, syntaxin, and synaptobrevin, which are critical to vesicular release or direct cleavage of inflammatory mediators including but not limited to SP, CGRP, PACAP, VIP" (First, col. 4, ll. 6-11).

12. First teaches that an "example whereby neurogenic inflammation takes place is in airway diseases, such as asthma, in which inflammatory

mediators such as cGRP and SP play a major role in the inflammatory process" (First, col. 4, ll. 57-60).

13. First teaches that the

> "[d]osage of the toxin is dependent on the area or condition that is to be treated. This could be as high as 1000 U but a more useful range of 5-500 LD50s of botulinum neurotoxin alone or in combination with other toxins, fusion proteins, peptides, or in combination with compounds such as capsaicin, may be more suitable. However higher or lower doses may be necessary.

(First, col. 7, ll. 22-28.)

14. MERCK teaches that Type I hypersentivity reactions involve antigens (allergens) that combine with specific IgE Antibodies that are bound to membrane receptors on tissue mast cells and blood basophiles (MERCK 318: 30-31).
15. MERCK teaches that this antibody (Ab) - antigen (Ag) "reaction causes the release of potent vasoactive and inflammatory mediators" (MERCK 318: 31-32).
16. MERCK teaches that Type I hypersensitivity reactions include allergic rhinitis, conjunctivitis, and asthma" (MERCK 319: 21).
17. MERCK teaches that Blepharitis is the inflammation of the eyelid margins (MERCK 2368: 13).
18. Appellant discloses that allergic blepharoconjunctivitis involves "conjunctival and lid margin erythema, itching and ocular mucous discharge associated with ocular irritation" (Spec. 16).

DISCUSSION

1. Claims 1, 5-8, 24, 25, 42, 43, and 46-57 stand rejected under the enablement provision of 35 U.S.C. § 112, first paragraph.

The Examiner finds that Appellant's Specification provides an enabling description of "a method of reducing allergy induced conjunctivitis in a mouse comprising administering a botulinum toxin", but does not provide an enabling description of "a method of reducing inflammation without causing muscle weakness" (Ans. 5). We disagree for the reasons the reasons set forth in Appellant's Brief (App. Br. 9-14).

However, to be complete, we recognize the Examiner's assertion that in all of "the human examples [in Appellant's Specification] the toxin is used in at least a dosage of 2.5 units . . . a dosage specifically *intended* to cause muscle weakness and the anti-inflammatory properties are merely observed as a side effect (see particularly Case I and Case II)" (Ans. 6). The human studies reported in Case I and Case II utilize a dosage of 2.5 units and 5 units of botulinum toxin per injection site respectively (Spec. 11 and 12). Contrary, to the Examiner's factually unsupported assertion, Appellant discloses that this dosage is lower than that required to produce regional muscle weakness (FF 1 and 2; App. Br. 10). Therefore, while the Examiner asserts that "[n]o where at pages 10 -20 [sic] does the specification disclose that Appellant actually measured for the claimed invention, i.e., a method of reducing inflammation without causing muscle weakness" (Ans. 13), the Examiner makes no attempt to provide an evidentiary basis to rebut Appellant's presumptively accurate disclosure. *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).

It is the Examiner who has the initial burden of establishing a prima facie case of non-enablement. The burden of proof does not shift to Appellant until the Examiner first meets his burden. *Marzocchi*, 439 F.2d at 223-224. For the foregoing reasons, we find that the Examiner has not met his burden of establishing a prima facie case of non-enablement. Accordingly, the rejection of claims 1, 5-8, 24, 25, 42, 43, and 46-57 under the enablement provision of 35 U.S.C. § 112, first paragraph is reversed.

2. Claims 1, 5-8, 10-12, 24, 25, and 42-57 stand rejected under the written description provision of 35 U.S.C. § 112, first paragraph.

While the Examiner asserts that Appellant's disclosure fails to adequately describe the claimed invention, the Examiner's statement of the rejection fails to identify or explain, with any degree of particularity, exactly what is not adequately described or the legal theory upon which the Examiner relies to support the rejection (*see* Ans. 8-10). It is not until the Examiner responds to the arguments presented in Appellant's Brief that the Examiner explains his position with any degree of particularity. Nevertheless, for the reasons set forth in Appellant's Brief we are not persuaded by the Examiner's assertions on this record (*see* App. Br. 20-37).

Accordingly, we reverse the rejection of claims 1, 5-8, 10-12, 24, 25, and 42-57 under the written description provision of 35 U.S.C. § 112, first paragraph.

3. Claims 10-12 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of First and MERCK.

First teaches a method to decrease or block inflammation induced by neurogenic mechanisms underlying or associated with inflammatory disorders by administering a safe and effective amount of Botulinum neurotoxin to antagonize the actions of neurogenic mediators involved in the disorder (FF 3-7 and 13; *see generally* Ans. 4). Appellant does not dispute and therefore concedes to this teaching in First. [3] Appellant does not dispute and therefore concedes to First's teaching that the immune system initiates, *inter alia*, the release of inflammatory mediators; and that a neurogenic disorder involves the release of mediators from, *inter alia*, the immune system (FF 8-9). Appellant does not dispute and therefore concedes to First's teaching that Substance P stimulates the release of immune-active agents resulting in a neuroendocrine cascade of events termed, neurogenic inflammation, and works as a central network modulating the events between the immune, nervous and endocrine systems; and that botulinum neurotoxin antagonizes this cascade of events (FF 9-11).

Appellant does, however, assert that First "differs from the claimed invention because it does not teach a method of reducing inflammation due to blepharoconjunctivitis, hay fever, rhinitis, or type 1 hypersensitivity[,] . . . allergic forms of eczema, urticaria or inflammatory bowel disease" (Reply Br. 6).

[3] Arguments not made are waived. *See* 37 C.F.R. § 41.37(c)(1)(vii) ("Any arguments or authorities not included in the brief or a reply brief ... will be refused consideration by the Board, unless good cause is shown.").

MERCK teaches that Type I hypersensitivity reactions involve allergens and causes the release of vasoactive and inflammatory mediators (FF 14-15). MERCK teaches that Type I hypersensitivity reactions include allergic rhinitis, *conjunctivitis*, and *asthma* (FF 16). First teaches that neurogenic inflammation takes place, *inter alia*, in *asthma*, wherein inflammatory mediators such as cGRP and SP play a major role in the inflammatory process (FF 12). Taken together, the combination of First and MERCK teach that *asthma* is a Type I hypersensitivity reaction that falls within the genus of neurogenic inflammation that is treatable by the administration of botulinum toxin.

MERCK teaches that Blepharitis is an inflammation of the eyelid margins and Appellant acknowledges that allergic blepharoconjunctivities involves both the conjunctival and lid margin (FF 17-18). Stated differently, blepharoconjunctivitis is the combination of *conjunctivitis* with blepharitis. Absent evidence to the contrary, of which there is none, we find that like asthma, *conjunctivitis* is a Type I hypersensitivity reaction that falls within the genus of neurogenic inflammation that is treatable by the administration of botulinum toxin as taught by First.

While Appellant does not provide an explicit statement of the claim groupings, it appears that Appellant has separately argued claims 10 and 12 (*see* App. Br. 19). Accordingly, we limit our discussion to claims 10 and 12. Claim 11 will stand or fall together with claim 12. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 10:

Claim 10 is drawn to a method for treating allergic blepharoconjunctivitis, which is combination of *conjunctivitis* with blepharitis. The claimed method comprises the single step of administering a therapeutically effective dose of a botulinum toxin in a periocular area of a subject suffering from blepharoconjunctivitis, thereby reducing inflammation. According to Appellant, the combination of First and MERCK fails to teach or suggest "'*allergic blepharoconjunctivitis*' or 'a periocular area' as required by claim 10" (App. Br. 19). We disagree.

As discussed above, absent evidence to the contrary, of which there is none, we find that *conjunctivitis* is a Type I hypersensitivity reaction that falls within the genus of neurogenic inflammation as taught by First. By reducing the inflammation of the conjunctivitis the inflammation in a subject suffering from blepharoconjunctivitis is reduced. In addition, First teaches a method of treating neurogenic inflammation by administering botulinum toxin at or near the site of inflammation (FF 5). For allergic blepharoconjunctivitis, the site of inflammation would be a periocular area.

For the foregoing reasons, we are not persuaded by Appellant's argument that the "specific limitations recited in the claim[ ] are not taught in the references" (App. Br. 19). Express teachings directed to the specific subject matter of a claim are not required to reach a conclusion of obviousness. *KSR Int'l. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (2007). As on this record,

> the teaching, motivation, or suggestion may be implicit from the prior art as a whole, rather than expressly stated in the references. . . . The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the

> art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art.

In re Kahn, 441 F.3d 977, 987-988 (Fed. Cir. 2006). Stated differently, "a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 127 S. Ct. at 1741.

On reflection, we find that the preponderance of the evidence on this record supports a conclusion that the claimed method would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made. For the foregoing reasons, we are not persuaded by Appellant's assertion that *KSR* is inapplicable to the facts on this record (Reply Br. 6).

Accordingly, we affirm the rejection of claim 10 under 35 U.S.C. § 103(a) as unpatentable over the combination of First and MERCK. However, because our rationale differs from the Examiner's we affirm this rejection as a new ground of rejection. 37 C.F.R. § 41.50(b).

Claim 12:

Claim 12 is drawn to a method for treating classic type 1 hypersensitivity comprising the step of administrating a botulinum toxin to an affected area of a subject suffering from classic type 1 hypersensitivity, thereby reducing inflammation, wherein the hypersensitivity is hay fever, rhinitis, allergic rhinitis, allergic forms of eczema, urticaria, rheumatoid arthritis, inflammatory bowel disease, or *asthma*.

According to Appellant, the combination of First and MERCK fails to teach "'hay fever,' 'allergic forms of eczema,' 'urticaria,' or 'inflammatory bowel disease'" (App. Br. 19). In this regard, Appellant asserts that

"[s]hould the Office maintain the instant rejection, Applicant respectfully requests that the Office specifically indicate where in the references cited in the rejection these teachings appear" (*id.*). We decline Appellant's request. Claim 12 is not limited to hay fever, allergic forms of eczema, urticaria, or inflammatory bowel disease. To the contrary, the Markush grouping set forth in claim 12 includes *asthma*.

A claimed invention is obvious "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). To make this determination, we consider, in the context of the knowledge and level of skill possessed by a person of ordinary skill in the art, whether such a person would have had reason to combine the prior art in the fashion claimed by the application at issue. *See KSR*, 127 S. Ct. at 1740-41. As discussed above, the combination of First and MERCK teach that *asthma* is a Type I hypersensitivity reaction that falls within the genus of neurogenic inflammation that is treatable by the administration of botulinum toxin. Accordingly, we find that the preponderance of the evidence on this record supports a conclusion that the claimed method would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made. For the foregoing reasons, we are not persuaded by Appellant's assertion to the contrary (App. Br. 19-20) or Appellant's assertion that *KSR* is inapplicable to the facts on this record (Reply Br. 6).

Accordingly, we affirm the rejection of claim 12 under 35 U.S.C. § 103(a) as unpatentable over the combination of First and MERCK. Claim 11 falls together with claim 12. However, because our rationale differs from the Examiner's we affirm this rejection as a new ground of rejection. 37 C.F.R. § 41.50(b).

CONCLUSION

In summary, we reverse the rejections under the enablement and written description provisions of 35 U.S.C. § 112, first paragraph.

We affirm the rejection of claims 10-12 under 35 U.S.C. § 103(a) as unpatentable over the combination of First and MERCK. However, because our rationale differs from that of the Examiner we affirm the rejection as a new ground of rejection. 37 C.F.R. § 41.50(b).

TIME PERIOD FOR RESPONSE

This decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 C.F.R. § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the appellant, *WITHIN TWO MONTHS FROM THE DATE OF THE DECISION*, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution*. Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .
>
> (2) *Request rehearing*. Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED-IN-PART

cdc

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